IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC., Plaintiff, v. MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC., Defendants.	)	C.A. No. 22-228 (RGA) (JLH) **CONSOLIDATED**

EXELIXIS' PROPOSED FINDINGS OF FACT
ON INFRINGEMENT OF U.S. PATENT NO. 11,298,349

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TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

Abbreviation	Description
’439 patent	U.S. Patent No. 11,091,439 (JTX-001)
’440 patent	U.S. Patent No. 11,091,440 (JTX-002)
’015 patent	U.S. Patent No. 11,098,015 (JTX-003)
’349 patent	U.S. Patent No. 11,298,349 (JTX-004)
1-1 impurity	6,7-dimethoxy-quinoline-4-ol
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
Asserted Claims	For the ’349 patent, claim 3 For the ’439 patent, claim 4 For the ’440 patent, claim 3 For the ’015 patent, claim 2
Exelixis	Exelixis, Inc.
FDA	United States Food and Drug Administration
FOF	Exelixis’ Proposed Findings of Fact on MSN’s Infringement
GRASTAR	Granulated corn starch
MSN	MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc.
MSN’s ANDA	MSN ANDA No. 213878
NDA	New Drug Application
POSA	Person of ordinary skill in the art
Tr.	Final Trial Transcripts
UF	Uncontested Facts (D.I. 154, Ex. 1)
Zydus	Zydus Worldwide DMCC

I. Background

1. Plaintiff Exelixis, Inc. ("Exelixis"), based in Alameda, California, first began investigating tyrosine kinase inhibitors as a potential cancer therapeutic in the early 2000s. Tr. 587:18-20 (Shah). Of the 5,000 compounds the company investigated and the fifteen taken into clinical trials, cabozantinib (L)-malate was the only one ultimately approved by the United States Food and Drug Administration ("FDA"). Tr. 587:21-588:8 (Shah).

2. After discovering the cabozantinib compound in 2003, Exelixis spent years developing a safe and effective pharmaceutical product. PTX-252 (Exelixis' patent claiming the compound with 2003 priority date); Tr. 571:22-572:1 (Wilson). Exelixis scientists investigated the free base and different salt forms of cabozantinib before concluding that cabozantinib (L)-malate had the most desirable properties for a successful clinical product. Tr. 589:24-597:9 (Shah). Exelixis also spent approximately eight years developing a safe and effective pharmaceutical formulation and discovering a synthetic process for making cabozantinib (L)-malate that would minimize a harmful genotoxic impurity that had been identified. Tr. 570:18-573:5, 576:13-24 (Wilson).

3. In 2012, Exelixis received approval for Cometriq® (cabozantinib (L)-malate) 20 mg and 80 mg capsules. UF ¶¶ 57-58; Tr. 588:4-8 (Shah). Cometriq® is indicated for the treatment of progressive, metastatic medullary thyroid cancer. UF ¶¶ 57, 58, 61; PTX-4. In 2016, Exelixis received approval for Cabometyx® (cabozantinib (L)-malate) 20, 40, and 60 mg tablets. UF ¶¶ 47-48; Tr. 588:9-13 (Shah). Cabometyx® is indicated for the treatment of kidney cancer, liver cancer, and differentiated thyroid cancer. UF ¶¶ 52-56; PTX-1; Tr. 944:21-946:3 (George). According to the June 2023 National Comprehensive Clinical Practice Guidelines, Cabometyx® is the "preferred" regimen for certain kidney cancer. Tr. 947:20-948:13 (George); PTX-528 at 15. Cometriq® and Cabometyx® have now been used to treat over 55,000 patients in

the United States alone, and have changed the landscape for cancer patients. Tr. 979:25-980:8, 981:17-980:8 (Tate); PTX-824; Tr. 949:7-21, 953:21-954:16, 957:11-19, 945:24-946:20 (George).

4. U.S. Patent Nos. 11,091,439 ("the '439 patent"), 11,091,440 ("the '440 patent"), and 11,098,015 ("the '015 patent") (collectively, "the Crystalline Malate Salt Patents") are directed to various aspects of Exelixis' discovery of the crystalline malate salt of cabozantinib (L)-malate. U.S. Patent No. 11,298,349 ("the '349 patent") is directed to a pharmaceutical composition of cabozantinib (L)-malate free of the genotoxic impurity 6,7-dimethoxy-quinoline-4-ol ("1-1 impurity"). The patents are owned by Exelixis and listed in FDA's *Orange Book* in connection with Cabometyx®. UF ¶¶ 26, 39, 62.

5. Defendants are MSN Laboratories Private Ltd. an Indian corporation based in Hyderabad, and its wholly owned subsidiary, MSN Pharmaceuticals Inc., a Delaware corporation based in New Jersey (collectively, "MSN"). UF ¶¶ 2, 3, 4.

6. In 2019, MSN submitted Abbreviated New Drug Application ("ANDA") No. 213878 to the FDA seeking approval for the commercial manufacture, use, and/or sale of 20 mg, 40 mg, and 60 mg cabozantinib tablets ("MSN ANDA Products") prior to the expiration of the '349, '439, '440, and '015 patents. UF ¶¶ 6, 63, 64.

II. Trial Witnesses Offering Testimony Relevant to Infringement of the '349 Patent

7. ***Dr. John Koleng, Ph.D.*:** Dr. Koleng, whom the Court recognized as an expert in pharmaceutical formulation, is Vice President of Product Development & Manufacturing at TFF Pharmaceuticals, Inc. in Austin, Texas and has over 30 years of experience in drug formulation, including for tablets and capsules. Tr. 70:7-21, 71:7-16 (Koleng); Tr. 72:16-29; PTX-777 at 1.

8. ***Dr. Maureen Donovan, Ph.D.*:** Dr. Donovan, whom the Court recognized as an expert in the field of pharmaceutics including solid dose drug formulation, is a professor at the University of Iowa. Tr. 184:23-24 (Donovan); Tr. 186:3-7.

9. ***Dr. Khalid Shah, Ph.D.*:** Dr. Shah is Senior Vice President of Pharmaceutical Operations, Manufacturing, and Supply Chain at Exelixis, and named inventor of the '349 patent. Tr. 586:17-21, 608:13-16 (Shah); JTX-004 at 1.

10. **Deposition Testimony:** Deposition testimony was introduced from: 1) ***Ravikumar Nithiyanandam***, Head of Formulations R&D at MSN (Tr. 59:4 et seq. (Nithiyanandam)); and 2) ***Dr. Jo Ann Wilson, Ph.D.***, former Vice President of Chemistry Manufacturing and Control at Exelixis and named inventor of the '349 patent. Tr. 564:7-10; Tr. 564:20-22; JTX-004 at 1.

III. Level of Ordinary Skill in the Art

11. A skilled artisan for the '349 patent would have had at least a bachelor's degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with several years of experience working in a pharmaceutical development and/or solid-state chemistry and would also have been part of a team which would have included synthetic organic chemists and process chemists, formulation scientists, analytical scientists and clinicians. Tr. 75:19-76:5 (Koleng).

12. MSN's expert relied on a similar definition of skilled artisan to Dr. Koleng's. Tr. 188:2-11 (Donovan). Both experts testified that their opinions concerning the '349 patent would not change based on the definition applied. Tr. 76:11-14 (Koleng); Tr. 188:12-14 (Donovan).

IV. The '349 Patent

13. Claim 3 of the '349 patent recites a pharmaceutical composition of cabozantinib (L)-malate that includes a filler, lubricant, disintegrant, and glidant, and is essentially free of the 1-1 impurity. JTX-004 at 34:30-51.

14. A pharmaceutical composition contains an active pharmaceutical ingredient ("API") combined with inactive ingredients called excipients. Tr: 76:22-77:3 (Koleng). Excipients can serve a variety of functions, such as facilitation of dose, manufacturing, and/or control of release, among others. Tr. 77:3-5 (Koleng).

15. A diluent, also referred to as a filler, is an excipient typically added to pharmaceutical compositions to increase bulk and facilitate handling. Tr. 78:12-18 (Koleng), Tr. 195:2-10, 247:6-11 (Donovan).

16. A disintegrant is an excipient added to a pharmaceutical composition that will physically break it up upon ingestion. Tr: 78:19-22 (Koleng).

17. A lubricant is an excipient added to a composition to reduce friction during manufacturing. Tr. 80:10-13 (Koleng).

18. MSN has stipulated that its ANDA products are pharmaceutical compositions (tablets) including a filler, disintegrant, and lubricant, and are essentially free of the 1-1 impurity. UF ¶¶ 65-70; Tr. 233:19-234:13 (Donovan). Infringement is established if MSN's ANDA Products are found to include a glidant. Tr. 234:14-17 (Donovan); Tr. 80:22-81:24 (Koleng).

19. A glidant is an excipient that improves the flow characteristics of a powder mixture, as Dr. Koleng, Dr. Donovan, and MSN's Mr. Nithiyanandam each testified. Tr. 82:9-11, 83:16-20, 84:21-85:3, 90:12-14 (Koleng); Tr. 230:16-19, 247:14-16 (Donovan); Tr. 60:2-4 (Nithiyanandam).

20. The two authorities on pharmaceutical compositions cited in the '349 patent specification provide similar definitions of a glidant. JTX-004 at 20:40-49; Tr. 82:15-84:25 (Koleng). "Remington: The Science and Practice of Pharmacy" ("Remington") defines a glidant as "a substance that improves the flow characteristics of a powder mixture." PTX-572A at 13; Tr. 83:10-20 (Koleng); Tr. 231:21-232:7 (Donovan) (referring to Remington's definition as "classic"). Swarbrick's "Encyclopedia of Pharmaceutical Technology" ("Swarbrick") states that "[g]lidant excipients improve the flow characteristic of tablet granulations (and capsule powder blends)." PTX-394 at 26; Tr. 84:7-84:25 (Koleng); Tr. 232:11-23 (Donovan).

21. The term glidant in the '349 patent does not require improvement of flow by any particular mechanism. Tr. 116:6-117:16 (Koleng); Tr. 230:16-19 (Donovan); JTX-004. Neither Claim 3 nor the specification of the '349 patent defines glidant with respect to a mechanism. Tr. 116:12-25 (Koleng); Tr. 230:25-231:2 (Donovan); JTX-004. The definitions of a glidant offered by Drs. Koleng and Donovan do not include a mechanism of action. Tr. 116:6-19, 117:3-16 (Koleng); Tr. 230:16-19 (Donovan). And neither Remington nor Swarbrick defines a glidant with respect to a specific mechanism. PTX-572A at 13; PTX-394 at 26; Tr. 116:12-16 (Koleng).

V. MSN's ANDA Products

22. MSN's ANDA submissions contain truthful statements about MSN's ANDA Products. Tr. 61:13-16 (Nithiyanandam); Tr. 339:24-340:14 (Donovan); DTX-215 at 1. One of the documents submitted to the FDA by MSN in connection with its ANDA was a Product Development Report ("PDR"), which summarizes the development of MSN's ANDA products. Tr. 235:6-11 (Donovan); Tr. 62:21-63:15 (Nithiyanandam).

A. MSN Told the FDA that Cabozantinib (L)-Malate Flows Poorly

23. In its PDR, MSN stated that cabozantinib (L)-malate "exhibits poor flow properties." DTX-215 at 34; Tr. 89:5-16 (Koleng); Tr. 60:5-61:7 (Nithiyanandam); Tr. 208:17-209:2, 235:15-19 (Donovan).

24. A poorly-flowing API can create several problems. For example, the flow of a drug mixture has a direct impact on the content uniformity of the tablets produced. Tr. 79:21-80:6 (Koleng). Without adequate flow in the drug mixture, the amount of API may vary from tablet to tablet, resulting in inconsistent dosing. Tr. 79:21-80:6 (Koleng). The flow of a drug mixture can also impact performance (dissolution) of the tablets. Tr. 79:21-80:6 (Koleng). Achieving consistency in drug mixtures is important. Tr. 1007:21-1008:5 (Mega).

25. A poorly flowing API would benefit from a careful selection of excipients and manufacturing process to improve flow. Tr. 89:14-16 (Koleng). Both parties' experts agreed that glidants may be added to improve flow. Tr. 89:7-16 (Koleng); Tr. 235:15-19 (Donovan).

B. MSN Uses GRASTAR in an Amount and Manner Typical for a Glidant

26. Starch and its derivatives are commonly used as glidants. Tr. 95:13-96:7, 98:8-11 (Koleng); Tr. 226:2-12, 237:7-9, 217:20-24 (Donovan); Tr. 1045:25-1046:2 (MSN's Counsel's answer to the Court's question during closing arguments). For example, the textbook on pharmaceutical formulation titled "Pharmaceutical Dosage Forms: Tablets" ("Lachman") identifies "starch" and "Starch 1500"[1] as "commonly used glidants." PTX-553A at 176, 178; Tr. 96:25-97:23 (Koleng). Both experts relied on Lachman. Tr. 379:14-19 (Donovan); Tr. 96:12-98:11 (Koleng).

[1] Starch 1500 is a brand name for pregelatinized corn starch, which is mechanically processed corn starch like GRASTAR. Tr. 97:12-19 (Koleng).

27. One of the excipients in MSN's ANDA Products is GRASTAR, a starch derivative known as granulated corn starch. Tr. 86:5-8, 96:6-7 (Koleng); Tr. 247:3-13 (Donovan); PTX-677 at 2. GRASTAR is "good flowing" and would be expected, even before experiments, to enhance the flowability of granules. Tr. 237:7-9, 217:20-24 (Donovan).

28. MSN incorporates GRASTAR in its ANDA Products at a concentration of 9.71% of the total drug mixture. PTX-677 at 3; Tr. 105:18-22 (Koleng); Tr. 201:21-22, 233:12-15 (Donovan). According to the scientific literature, the typical concentration range for starch glidants is between 1.0 and 10.0%. Tr. 97:24-98:7, 105:18-106:5 (Koleng); Tr. 232:24-233:15 (Donovan); PTX-394 at 44. For example, Swarbrick and Lachman both describe starch being used as a glidant at a range between 1 and 10%. PTX-394 at 44; PTX-553A at 105; Tr. 95:4-10, Tr. 98:2-11 (Koleng); Tr. 232:24-233:11 (Donovan).

29. The 9.71% concentration at which GRASTAR is used in the MSN formulation supports the conclusion that GRASTAR is a glidant in MSN's ANDA Products. Tr. 104:18-105:5, 106:6-13 (Koleng).

30. As set forth in its PDR, the multistep process for manufacturing MSN's ANDA Products includes wet granulation. DTX-215 at 97-98; Tr. 103:21-24, 110:18-110:22 (Koleng); Tr. 62:13-20 (Nithiyanandam); Tr. 192:25-193:24 (Donovan). Powder materials including the cabozantinib, two diluents, and a portion of the disintegrant are de-lumped and sifted. DTX-215 at 97; Tr. 103:13-20 (Koleng); PDX-2 at 14. The powders are then mixed with a binder solution, dissolved in water, and dried to formed granules. DTX-215 at 97; Tr. 103:21-104:2 (Koleng); PDX-2 at 14.

31. Once the granules are formed, extragranular excipients are added. DTX-215 at 97; Tr. 104:2-5 (Koleng); PDX-2 at 14. During the pre-lubrication phase, the granules are mixed

with granulated corn starch (GRASTAR) and additional disintegrant. DTX-215 at 97; Tr. 104:2-14 (Koleng); Tr. 193:9-24 (Donovan); PDX-2 at 14. A lubricant is then added, and the final mixture is compressed into tablets and coated. DTX-215 at 97-98; Tr. 103:21-104:9 (Koleng); Tr. 246:20-23 (Donovan); PDX-2 at 14.

32. Although wet granulation can improve flowability of the overall drug mixture, (Tr. 110:23-111:1 (Koleng); Tr. 192:11-21 (Donovan); Tr. 609:22-610:23 (Shah)), glidants are often used after wet granulation to further improve flow, especially where the granules are fine. Tr. 111:2-14 (Koleng); Tr. 246:17-247:2 (Donovan).

33. Glidants are typically added after granulation, during the pre-lubrication stage of the tablet manufacturing process. Tr. 228:19-23, 246:20-247:2 (Donovan); *see also* Tr. 83:21-84:3 (Koleng); PTX-572A at 893. Exelixis adds a glidant during the pre-lubrication step after wet granulation in manufacturing the Cabometyx® tablets. Tr. 609:15-21, 610:10-23 (Shah).

34. MSN incorporates the GRASTAR component in its ANDA Products during the pre-lubrication step, just prior to compression. DTX-215 at 97; Tr. 86:12-16 (Koleng).

35. The stage at which MSN incorporates GRASTAR in its ANDA Products supports the conclusion that GRASTAR is a glidant. Tr. 102:5-11, 104:23-105:5 (Koleng).

C. MSN Told the FDA That GRASTAR Played an "Important Role in Flow Characteristics"

36. In the Initial Risk Assessment of its PDR, MSN submitted a table describing the materials used in its ANDA Products. DTX-215 at 34. This type of table is typically generated once a core formulation has been identified. Tr. 91:12-92:5 (Koleng). In the section of the table concerning GRASTAR, MSN stated (in the present tense) that "Granulated Corn Starch is used as a diluent in minimal concentration and it enhances the flowability of the granules." DTX-215

at 36; Tr. 61:17-20 (Nithiyanandam); Tr. 90:5-14 (Koleng); Tr. 227:14-17, 236:11-16 (Donovan). MSN has not withdrawn this statement. Tr. 62:10-12 (Nithiyanandam).

37. MSN's statement to the FDA that "Granulated Corn Starch… enhances the flowability of the granules" supports the conclusion that GRASTAR is a glidant in MSN's ANDA Products. Tr. 90:5-14 (Koleng).

38. In the Formula Optimization section of the PDR, MSN described a study regarding optimization of the level of GRASTAR. DTX-215 at 53; Tr. 62:21-24 (Nithiyanandam). Specifically, MSN studied formulations of generic cabozantinib (L)-malate with concentrations of GRASTAR ranging from 6.7% to 12.7%. DTX-215 at 60.

39. In the section of its PDR describing these experiments, MSN stated that "[t]he level of Granulated corn Starch plays an important role in flow characteristics." DTX-215 at 58; Tr. 92:11-16, 114:14-21 (Koleng). MSN's Head of Formulation Research and Development confirmed that this statement in MSN's PDR was based on the studies done by MSN. Tr. 63:13-15 (Nithiyanandam). MSN was not merely characterizing the literature on granulated corn starch. Tr. 62:21-63:15 (Nithiyanandam); Tr. 235:6-11 (Donovan).

40. MSN's statement to the FDA that "[t]he level of Granulated corn Starch plays an important role in flow characteristics" supports the conclusion that GRASTAR is a glidant in MSN's ANDA Products. Tr. 92:11-93:1 (Koleng).

41. MSN's Justification for Microbial Method Validation states that MSN evaluated the quality of three grades of corn starch, and explicitly included GRASTAR. PTX-724 at 1; Tr. 100:12-21 (Koleng). MSN wrote: "Starch are [sic] used in pharmaceutical industry for a wide variety of reasons, such as an excipient in tablet and capsule [sic] as a diluent, as a glidant or as binder." PTX-724 at 1-2; Tr. 99:24-100:4, 101:3-14 (Koleng).

42. MSN's statement to the FDA in the Justification for Microbial Method Validation supports the conclusion that GRASTAR is a glidant in MSN's ANDA Products. Tr. 101:5-20 (Koleng).

43. MSN's statements to the FDA regarding the glidant activity of GRASTAR are also confirmed by the scientific literature indicating that GRASTAR can be a glidant. Tr. 101:15-20, 95:13-96:7, 98:8-11, 96:25-23 (Koleng); PTX-553A at 176, 178. And testing done by GRASTAR's manufacturer confirmed that that its granulated corn starch resulted in a "flowability improvement" of a poorly flowing API. PTX-447 at 2; Tr. 119:15-121:23 (Koleng).

D. MSN's Contention that GRASTAR Is Not a Glidant Is Not Supported by Evidence

1. The Concentration of GRASTAR in MSN's ANDA Products Would Not Have Meaningful Impact as a Diluent

44. MSN describes GRASTAR as a diluent in its ANDA. Tr. 201:16-20 (Donovan); DTX-215 at 28. But GRASTAR is used in such a minimal concentration (9.71%) that it would not have a meaningful impact as a diluent. Tr. 91:1-8 (Koleng).

45. In any event, excipients can have more than one function in a mixture. Tr. 247:12-13 (Donovan); Tr. 179:25-180:4, 90:15-25, 93:2-6 (Koleng). An excipient can be both a glidant and a diluent. Tr. 93:2-6, 90:15-25 (Koleng); Tr. 247:12-22 (Donovan).

2. GRASTAR Did Not Improve the Dissolution of MSN's ANDA Products

46. A study in MSN's PDR compared dissolution rates of formulations with varying levels of GRASTAR in the drug mixture: "low" (6.7%), "optimum" (9.7%), and "high" (12.70%) concentrations. DTX-215 at 60; Tr. 63:20-64:19 (Nithiyanandam); Tr. 113:2-114:4 (Koleng). This study concluded that: "Based on the above results, no significant difference was observed in the dissolution profiles of cabozantinib tablets" with varying levels of GRASTAR. DTX-215 at 60; Tr. 215:14-19 (Donovan). MSN's own testing thus demonstrates that nearly

doubling the concentration of GRASTAR did not have an impact on dissolution. DTX-215 at 60; Tr. 112:6-113:8, 114:5-13 (Koleng); Tr. 215:14-19 (Donovan).

3. GRASTAR Improves Flow Through MSN's Proposed Glidant Mechanisms

47. MSN's expert Dr. Donovan proposed five mechanisms through which a glidant is purported to improve flow: (1) reducing electrostatic forces; (2) adsorbing fine particles; (3) absorbing environmental gases; (4) reducing van der Waals interactions; and (5) coating / adherence. Tr. 199:21-200:8, 217:25-218:4 (Donovan); PDX-2.20 at 20.

48. Although it is not necessary to prove that a glidant is improving flow through any particular mechanism (*see supra* ¶ 21), it is more likely than not that GRASTAR acts through one or more of MSN's proposed mechanisms. Tr. 117:8-23, 116:6-25 (Koleng).

a. GRASTAR Improves Flow by Reducing Electrostatic Forces

49. Electrostatic forces refer to electrical friction between particles. Tr. 118:2-6 (Koleng). GRASTAR more likely than not improves flow in MSN's ANDA Products by reducing electrostatic forces by facilitating uniform mixing and distributing electrical charges in the mixture. Tr. 118:7-15 (Koleng). GRASTAR also has sufficient water content to dissipate charges. Tr. 118:7-15 (Koleng).

b. GRASTAR Improves Flow by Adsorbing Fine Particles

50. Adsorbing fine particles is a mechanism by which a glidant can adhere to fine particles in the mixture that impede flow, thereby facilitating flow. Tr. 118:16-119:1 (Koleng); Tr. 220:1-11 (Donovan). GRASTAR more likely than not improves flow in MSN's ANDA Products by adsorbing fine particles due to its structure and porous surface. Tr. 119:2-10 (Koleng).

51. The manufacturer of GRASTAR performed experiments that led it to conclude that GRASTAR improved the flowability of the poorly flowing drug substance fenofibrate.

PTX-447 at 2; Tr. 119:14-120:1, 120:16-17 (Koleng). The manufacturer attributed the "flowability improvement" to "more effective reduction of fenofibrate interparticle cohesion in GRASTAR," possibly because "most of the small fenofibrate particles can preferably adhere to the void space of GRASTAR particles' surfaces, rather than adhere to themselves." PTX-447 at 2; Tr. 120:12-25 (Koleng). This document from the manufacturer of GRASTAR supports the conclusion that GRASTAR improves flow in MSN's ANDA Products by adsorbing fine particles. Tr. 121:4-23 (Koleng); PTX-447.

c. GRASTAR Improves Flow by Absorbing Environmental Gases

52. A glidant can improve flow by absorbing gases, such as air or water vapor, which if not absorbed can cause the powder blend to resist flow. Tr. 122:2-6 (Koleng). GRASTAR more likely than not improves flow in MSN's ANDA Products by absorbing gases, because corn starch and starch derivatives are hygroscopic, which means they will preferentially absorb water or moisture in a mixture, thereby rendering it more flowable. Tr. 122:7-15 (Koleng).

d. GRASTAR Improves Flow by Reducing Van Der Waals Forces

53. Van der Waals forces refer to the attractive forces between the particles in a mixture. Tr. 122:16-21 (Koleng). One of the ways to reduce those inter-particle attractions is to incorporate a spacer that physically separates the particles. Tr. 122:16-123:5 (Koleng); Tr. 248:6-9 (Donovan). GRASTAR acts as a spacer that physically separates the particles from one another and thereby more likely than not reduces van der Waals forces. Tr. 122:22-123:5 (Koleng); Tr. 248:16-20 (Donovan).

e. GRASTAR Improves Flow by Coating / Adherence

54. Coating / adherence is a mechanism by which a glidant can absorb or stick onto the surface of larger materials, smooth out irregularities, and reduce friction between particles. Tr. 123:6-11 (Koleng); Tr. 218:5-15 (Donovan). GRASTAR very likely improves flow in

MSN's ANDA Products by coating / adherence because after granulation of the drug mixture, there are still particles left that are larger than the GRASTAR particles. Tr. 123:12-20 (Koleng). GRASTAR can adhere to the surface of the larger particles, smoothing out the mixture and rendering it more flowable. Tr. 123:16-20 (Koleng).

4. MSN's Laboratory Notebook Data Is Unreliable

55. A laboratory notebook produced by MSN ("Laboratory Notebook No. 252") includes a purported comparison between two prototype cabozantinib formulations—one with unmodified corn starch in the extragranular layer and another with GRASTAR in the extragranular layer. DTX-196 at 46-48, 84-86; Tr. 134:2-135:3 (Koleng).

56. Laboratory Notebook No. 252 records numerical values for bulk density, tap density, Carr Index and Hausner ratio for these two prototype formulations. DTX-196 at 46-48, 84-86; Tr. 136:7-11, 182:12-14 (Koleng); Tr. 251:23-252:21 (Donovan). Bulk and tap density data are used to calculate Carr Index and Hausner ratios, which are common measurements of flow characteristics. Tr. 131:3-7 (Koleng).

57. However, there is an error of unidentified origin in the recorded numbers. Tr. 107:3-19, 127:22-128:4, 181:16-182:7 (Koleng). The inputs do not match the recorded results. Tr. 107:3-11 (Koleng).

58. Due to this error, it is not possible to determine from MSN's prototype study how replacing GRASTAR with unmodified corn starch in the extragranular layer affected flow. Tr. 181:16-182:7 (Koleng); Tr. 1068:3-23. Dr. Donovan did not address the discrepancy in the data from Laboratory Notebook No. 252 in her testimony. Tr. 211:17-25 (Donovan).

59. Even if the Carr index and Hausner ratio data in Laboratory Notebook No. 252 were reliable, it would only show that GRASTAR is not as effective a glidant as unmodified corn starch, another well-documented glidant in the literature, in this particular prototype

formulation. Tr. 182:8-14, 101:8-14, 95:21-96:5, 98:8-11 (Koleng); Tr. 1046:3-17 (Court's questions to MSN's Counsel during closing).

VI. MSN Had Knowledge of the '349 Patent and Knows that MSN's ANDA Products Infringe

60. MSN has entered into a license and supply agreement with Zydus, whereby MSN has agreed to supply Zydus with MSN's ANDA Products for importation and sale in the United States. UF ¶ 71; PTX-744; Tr. 125:17-126:5 (Koleng). MSN's label encourages doctors to prescribe and patients to use MSN's ANDA Products in the United States. PTX-698; Tr. 125:3-7 (Koleng).

61. MSN was aware of the '349 patent when MSN chose to pursue a generic version of Exelixis' cabozantinib (L)-malate drug product. UF ¶ 9 (MSN sent a Paragraph IV certification letter to Exelixis on June 6, 2022); Tr. 126:6-126:17 (Koleng). MSN was and is aware of Exelixis' particularized infringement allegations, which are based on MSN's own admissions to the FDA in its ANDA. Tr. 126:6-126:17, 107:23-108:6 (Koleng).

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December 12, 2023

CERTIFICATE OF SERVICE

I hereby certify that on December 12, 2023, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on December 12, 2023, upon the following in the manner indicated:

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